REMARKS/ARGUMENTS

Claims 58-65, 68-70 and 74-77 are pending in this application. Claims 63-65 and 68-70 are allowed.

Applicants note and thank the Examiner for withdrawal of previous objections and rejections under 35 U.S.C. §112, first and second paragraphs.

Priority

Applicants note that the effective filing date of the present application is March 8, 1999.

Utility

Applicants note that utility is established based on Example 109, Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assay 9).

Claim Rejections – 35 U.S.C. §112, First Paragraph (Enablement)

Claims 58-62 and 74-77 remain rejected under 35 U.S.C. §112, first paragraph, allegedly "because the specification, while being enabling for SEQ ID NO:118 which encodes SEQ ID NO:119 exemplified as exhibiting activity EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assay 9) at p. 326, does not reasonably provide enablement for the variable polynucleotide and peptide sequences and for such generic sequences where no requisite functional activity is provided as claimed." The Examiner further asserts that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims."

Applicants respectfully disagree and traverse the rejection.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation.[1] [2] Accordingly, the test for

---

[1] MPEP §2164.0120

enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[3] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[4, 5]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include: 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important."[6, 7] "Limitations and examples in the specification do not generally limit what is covered by the claims" MPEP § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[8]

---

[2] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998).

[3] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)

[4] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)

[5] MPEP §2164.06.

[6] MPEP §2164.08

[7] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971)

[8] *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

The Disclosure provides sufficient information to enable the claimed invention

Claims 58-62 and 74-77 are directed to a genus of nucleic acid sequences encoding polypeptides which are at least 80-99% identical to the amino acid sequence of the polypeptide of SEQ ID NO:119 and which have a specific and useful function (*i.e.* to a genus of polypeptides that inhibit endothelial cell growth).

Applicants respectfully maintain the position that Claims 58-62 and 74-77 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' response filed on November 29, 2004.

As previously stated in the Applicants' response filed on November 29, 2004, Claims 58-62 (and, as a consequence, those claims dependent from the same) recite a polypeptide that inhibits endothelial cell growth. Therefore, the claimed genus is characterized by a combination of structural and functional features and any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made.

Applicants have provided nucleic acid sequence SEQ ID NO:118 and the polypeptide sequence SEQ ID NO:119. Further, the Examiner has acknowledged that the specification is enabling for SEQ ID NO:118 which encodes SEQ ID NO:119.

Example 109 of the present application provides step-by-step guidelines and protocols for testing polypeptides that are useful for inhibiting endothelial cell growth in mammals. By following the disclosure in the specification, one skilled in the art can easily determine whether a variant PRO320 protein has tested positive for inhibiting endothelial cell growth in mammals. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PRO320 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specifications sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward). Accordingly, one skilled in the art given the disclosure in the specification would be able to make the claimed nucleic acid sequences

encoding the variant amino acid sequences having the claimed biological function. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:119. Accordingly, one of ordinary skill could practice the claimed invention without undue experimentation.

The Examiner alleges, "The specification does not enable this broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not each which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke activity." (See page 5 of instant Office Action).

Applicants respectfully disagree. As indicated above, given the specification, one skilled in the art could readily identify variants of PRO320 sequence. It would be a simple matter for one skilled in the art to test the variant PRO320 protein to determine whether it can inhibit endothelial cell growth using the assay described in Example 109. This would not require undue experimentation. Furthermore, once such an amino acid sequence is identified, one skilled in the art could easily determine the nucleic acid sequences which would encode such amino acid sequence. As discussed above, a considerable amount of experimentation is permissible, if it is merely routine.

For the above-noted reasons, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. §102

Claims 58-62 remain rejected under 35 U.S.C. 102(e) as being anticipated by Ford *et al.*, U.S. Patent No. 6,392,018, filed February 12, 1999 and issued May 21, 2002.

In particular, the Examiner alleges that Declaration filed on November 29, 2004 is not persuasive because it is unexecuted.

Applicants respectfully submit that signed Declarations under 37 C.F.R. §1.131 by Dr. Ferrara, Dr. Goddard, Dr. Godowski, Dr. Gurney and Dr. Wood were submitted with a Supplemental Response to Office Action filed on February 10, 2005, copies of which are enclosed herewith for the Examiner's review. The consideration of the signed Declarations is respectfully requested.

Applicants note that the Supplemental Response along with the executed Declarations filed on February 10, 2005 are clearly of record as shown in the Patent Application Information Retrieval (PAIR) system on the USPTO website.

As stated in the Declarations, Applicants had obtained PRO320 polypeptide and had examined the effect of this polypeptide on the endothelial cell proliferation in the United States prior to February 12, 1999. Accordingly, the Declarations clearly show that the invention claimed in the present application was conceived and reduced to practice prior to February 12, 1999. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C62**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: April 25, 2005

By: _____
Anna L. Barry (Reg. No. 51,436)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2120196 v1
4/23/05 4:13 PM (39780.2630)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Turner, Sharon L.
Avi J. ASHKENAZI, et al.	)	Art Unit: 1647
Application Serial No. 10/017,191	)	Confirmation No: 6712
Filed: October 24, 2001	)	Attorney's Docket No. 39780-2630 P1C62
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

DECLARATION OF NAPOLEONE FERRARA, Ph.D., AUDREY GODDARD, Ph.D., PAUL J. GODOWSKI, Ph.D., AUSTIN GURNEY, Ph.D., AND WILLIAM I. WOOD, Ph.D. UNDER 37 C.F.R. §1.131

MAIL STOP AMENDMENT
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Napoleone Ferrara, Ph.D., Audrey Goddard, Ph.D., Paul J. Godowski, Ph.D., Austin Gurney, Ph.D., and William I. Wood, Ph.D. declare and say as follows:

1. We are the inventors of the above-identified application.

2. We have read and understood the claims pending in this application, and are aware that the claims have been rejected as anticipated by Ford *et al.*, U.S. Patent No. 6,392,018, filed February 12, 1999 and issued May 21, 2002.

3. We conceived and reduced to practice the invention claimed in the above-identified application in the United States prior to February 12, 1999.

4. At the time the present invention was made, one of the inventors, Napoleone Ferrara, Ph.D., was, as still is, responsible for overseeing the testing of novel polypeptides, including the polypeptide designated PRO320, in endothelial cell proliferation assay (Assay #9, Example 109). This assay is used to find agents that are capable of inhibiting proliferation of endothelial cells.

5. In this assay, bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum 12-14 passages) were plated on 96 well plates at a density of 500 CELLS/WELL per 100 L in low glucose DMEM, 10% calf serum. 2 mM glutamine, lx pen/strept and fungizone, supplemented with 3 ng/mL VEGF. Controls were plated the same way but some did not include VEGF. A test sample of the PRO polypeptide of interest was added in a 100 111 volume for a 200 UL FINAL VOLUME. Cells were incubated for 6-7 days at 37°C. The media was aspirated and the cells washed lx with PBS. An acid phosphatase reaction mixture (100 YL, 0. IM sodium acetate, pH 5.5,0.1 % TRITON-100,10 mM p-nitrophenyl phosphate) was added. After incubation for 2 hours at 37°C, the reaction was stopped by addition of 10 JAL IN NaOH. OD was measured on microtiter plate reader at 405 nm. Controls were no cells, cells alone, cells + FGF (5 NG/ML), cells + VEGF (3 NG/ML), cells + VEGF (3 ng/ml) + TGF-ß (1 ng/ml), and cells + VEGF (3ng/mL) + LIF (5 NG/ML). (TGF-P at a I ng/ml concentration is known to block 70-90% of VEGF stimulated cell proliferation.) The results were assessed by calculating the percentage inhibition of VEGF (3 ng/ml) stimulated cells proliferation, determined by measuring acid phosphatase activity at OD405 NM. (1) relative to cells without stimulation, and (2) relative to the reference TGF-ß inhibition of VEGF stimulated activity. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis.

6. Copies of pages from laboratory notebook showing the positive results for the PRO320 polypeptide (SEQ ID NO:140), identified by Pin number P288-1, in Assay #9 are attached to this declaration (with dates redacted) as Exhibit A. These experiments were performed and the results were obtained prior to February 12, 1999.

7. Exhibit A clearly shows that the polypeptide designated PRO320 was tested, and its ability to inhibit the proliferation of endothelial cells was determined prior to February 12, 1999.

8. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Napoleone Ferrara	JAN-25-05 Date
Audrey Goddard	Jan. 3/05. Date
Paul J. Godowski	Date
Austin Gurney	Date
William I. Wood	Date

SV 2083152 v1
12/20/04 4:15 PM (39780.2630)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Turner, Sharon L.
	)	
Avi J. ASHKENAZI, et al.	)	Art Unit: 1647
	)	
Application Serial No. 10/017,191	)	Confirmation No: 6712
	)	
Filed: October 24, 2001	)	Attorney's Docket No. 39780-2630 P1C62
	)	
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

DECLARATION OF NAPOLEONE FERRARA, Ph.D., AUDREY GODDARD, Ph.D., PAUL J. GODOWSKI, Ph.D., AUSTIN GURNEY, Ph.D., AND WILLIAM I. WOOD, Ph.D. UNDER 37 C.F.R. §1.131

MAIL STOP AMENDMENT
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Napoleone Ferrara, Ph.D., Audrey Goddard, Ph.D., Paul J. Godowski, Ph.D., Austin Gurney, Ph.D., and William I. Wood, Ph.D. declare and say as follows:

1. We are the inventors of the above-identified application.

2. We have read and understood the claims pending in this application, and are aware that the claims have been rejected as anticipated by Ford *et al.*, U.S. Patent No. 6,392,018, filed February 12, 1999 and issued May 21, 2002.

3. We conceived and reduced to practice the invention claimed in the above-identified application in the United States prior to February 12, 1999.

4. At the time the present invention was made, one of the inventors, Napoleone Ferrara, Ph.D., was, as still is, responsible for overseeing the testing of novel polypeptides, including the polypeptide designated PRO320, in endothelial cell proliferation assay (Assay #9, Example 109). This assay is used to find agents that are capable of inhibiting proliferation of endothelial cells.

5. In this assay, bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum 12-14 passages) were plated on 96 well plates at a density of 500 CELLS/WELL per 100 L in low glucose DMEM, 10% calf serum. 2 mM glutamine, lx pen/strept and fungizone, supplemented with 3 ng/mL VEGF. Controls were plated the same way but some did not include VEGF. A test sample of the PRO polypeptide of interest was added in a 100 111 volume for a 200 UL FINAL VOLUME. Cells were incubated for 6-7 days at 37°C. The media was aspirated and the cells washed lx with PBS. An acid phosphatase reaction mixture (100 YL, 0. IM sodium acetate, pH 5.5,0.1 % TRITON-100,10 mM p-nitrophenyl phosphate) was added. After incubation for 2 hours at 37°C, the reaction was stopped by addition of 10 JAL IN NaOH. OD was measured on microtiter plate reader at 405 nm. Controls were no cells, cells alone, cells + FGF (5 NG/ML), cells + VEGF (3 NG/ML), cells + VEGF (3 ng/ml) + TGF-ß (1 ng/ml), and cells + VEGF (3ng/mL) + LIF (5 NG/ML). (TGF-P at a I ng/ml concentration is known to block 70-90% of VEGF stimulated cell proliferation.) The results were assessed by calculating the percentage inhibition of VEGF (3 ng/ml) stimulated cells proliferation, determined by measuring acid phosphatase activity at OD405 NM. (1) relative to cells without stimulation, and (2) relative to the reference TGF-ß inhibition of VEGF stimulated activity. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis.

6. Copies of pages from laboratory notebook showing the positive results for the PRO320 polypeptide (SEQ ID NO:140), identified by Pin number P288-1, in Assay #9 are attached to this declaration (with dates redacted) as Exhibit A. These experiments were performed and the results were obtained prior to February 12, 1999.

7. Exhibit A clearly shows that the polypeptide designated PRO320 was tested, and its ability to inhibit the proliferation of endothelial cells was determined prior to February 12, 1999.

8. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Napoleone Ferrara	Date
Audrey Goddard	Jan. 3/05 Date
Paul J. Godowski	Date
Austin Gurney	Date
William I. Wood	Date

SV 2083152 v1
12/20/04 4:15 PM (39780.2630)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Turner, Sharon L.
	)	
Avi J. ASHKENAZI, et al.	)	Art Unit: 1647
	)	
Application Serial No. 10/017,191	)	Confirmation No: 6712
	)	
Filed: October 24, 2001	)	Attorney's Docket No. 39780-2630 P1C62
	)	
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

DECLARATION OF NAPOLEONE FERRARA, Ph.D., AUDREY GODDARD, Ph.D., PAUL J. GODOWSKI, Ph.D., AUSTIN GURNEY, Ph.D., AND WILLIAM I. WOOD, Ph.D. UNDER 37 C.F.R. §1.131

MAIL STOP AMENDMENT
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Napoleone Ferrara, Ph.D., Audrey Goddard, Ph.D., Paul J. Godowski, Ph.D., Austin Gurney, Ph.D., and William I. Wood, Ph.D. declare and say as follows:

1. We are the inventors of the above-identified application.

2. We have read and understood the claims pending in this application, and are aware that the claims have been rejected as anticipated by Ford *et al.*, U.S. Patent No. 6,392,018, filed February 12, 1999 and issued May 21, 2002.

3. We conceived and reduced to practice the invention claimed in the above-identified application in the United States prior to February 12, 1999.

4. At the time the present invention was made, one of the inventors, Napoleone Ferrara, Ph.D., was, as still is, responsible for overseeing the testing of novel polypeptides, including the polypeptide designated PRO320, in endothelial cell proliferation assay (Assay #9, Example 109). This assay is used to find agents that are capable of inhibiting proliferation of endothelial cells.

5. In this assay, bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum 12-14 passages) were plated on 96 well plates at a density of 500 CELLS/WELL per 100 L in low glucose DMEM, 10% calf serum. 2 mM glutamine, lx pen/strept and fungizone, supplemented with 3 ng/mL VEGF. Controls were plated the same way but some did not include VEGF. A test sample of the PRO polypeptide of interest was added in a 100 111 volume for a 200 UL FINAL VOLUME. Cells were incubated for 6-7 days at 37°C. The media was aspirated and the cells washed lx with PBS. An acid phosphatase reaction mixture (100 YL, 0. IM sodium acetate, pH 5.5,0.1 % TRITON-100,10 mM p-nitrophenyl phosphate) was added. After incubation for 2 hours at 37°C, the reaction was stopped by addition of 10 JAL IN NaOH. OD was measured on microtiter plate reader at 405 nm. Controls were no cells, cells alone, cells + FGF (5 NG/ML), cells + VEGF (3 NG/ML), cells + VEGF (3 ng/ml) + TGF-ß (1 ng/ml), and cells + VEGF (3ng/mL) + LIF (5 NG/ML). (TGF-P at a I ng/ml concentration is known to block 70-90% of VEGF stimulated cell proliferation.) The results were assessed by calculating the percentage inhibition of VEGF (3 ng/ml) stimulated cells proliferation, determined by measuring acid phosphatase activity at OD405 NM. (1) relative to cells without stimulation, and (2) relative to the reference TGF-ß inhibition of VEGF stimulated activity. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis.

6. Copies of pages from laboratory notebook showing the positive results for the PRO320 polypeptide (SEQ ID NO:140), identified by Pin number P288-1, in Assay #9 are attached to this declaration (with dates redacted) as Exhibit A. These experiments were performed and the results were obtained prior to February 12, 1999.

7. Exhibit A clearly shows that the polypeptide designated PRO320 was tested, and its ability to inhibit the proliferation of endothelial cells was determined prior to February 12, 1999.

8. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Napoleone Ferrara	Date
Audrey Goddard	Jan. 3/05 Date
Paul J. Godowski	1/25/05 Date
Austin Gurney	Date
William I. Wood	Date

SV 2083152 v1
12/20/04 4:15 PM (39780.2630)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Turner, Sharon L.
	)	
Avi J. ASHKENAZI, et al.	)	Art Unit: 1647
	)	
Application Serial No. 10/017,191	)	Confirmation No: 6712
	)	
Filed: October 24, 2001	)	Attorney's Docket No. 39780-2630 P1C62
	)	
For: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME	)	**Customer No. 35489**

DECLARATION OF NAPOLEONE FERRARA, Ph.D., AUDREY GODDARD, Ph.D., PAUL J. GODOWSKI, Ph.D., AUSTIN GURNEY, Ph.D., AND WILLIAM I. WOOD, Ph.D. UNDER 37 C.F.R. §1.131

MAIL STOP AMENDMENT
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Napoleone Ferrara, Ph.D., Audrey Goddard, Ph.D., Paul J. Godowski, Ph.D., Austin Gurney, Ph.D., and William I. Wood, Ph.D. declare and say as follows:

1. We are the inventors of the above-identified application.

2. We have read and understood the claims pending in this application, and are aware that the claims have been rejected as anticipated by Ford *et al.*, U.S. Patent No. 6,392,018, filed February 12, 1999 and issued May 21, 2002.

3. We conceived and reduced to practice the invention claimed in the above-identified application in the United States prior to February 12, 1999.

4. At the time the present invention was made, one of the inventors, Napoleone Ferrara, Ph.D., was, as still is, responsible for overseeing the testing of novel polypeptides, including the polypeptide designated PRO320, in endothelial cell proliferation assay (Assay #9, Example 109). This assay is used to find agents that are capable of inhibiting proliferation of endothelial cells.

5. In this assay, bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum 12-14 passages) were plated on 96 well plates at a density of 500 CELLS/WELL per 100 L in low glucose DMEM, 10% calf serum. 2 mM glutamine, lx pen/strept and fungizone, supplemented with 3 ng/mL VEGF. Controls were plated the same way but some did not include VEGF. A test sample of the PRO polypeptide of interest was added in a 100 111 volume for a 200 UL FINAL VOLUME. Cells were incubated for 6-7 days at 37°C. The media was aspirated and the cells washed lx with PBS. An acid phosphatase reaction mixture (100 YL, 0. IM sodium acetate, pH 5.5,0.1 % TRITON-100,10 mM p-nitrophenyl phosphate) was added. After incubation for 2 hours at 37°C, the reaction was stopped by addition of 10 JAL IN NaOH. OD was measured on microtiter plate reader at 405 nm. Controls were no cells, cells alone, cells + FGF (5 NG/ML), cells + VEGF (3 NG/ML), cells + VEGF (3 ng/ml) + TGF-ß (1 ng/ml), and cells + VEGF (3ng/mL) + LIF (5 NG/ML). (TGF-P at a I ng/ml concentration is known to block 70-90% of VEGF stimulated cell proliferation.) The results were assessed by calculating the percentage inhibition of VEGF (3 ng/ml) stimulated cells proliferation, determined by measuring acid phosphatase activity at OD405 NM. (1) relative to cells without stimulation, and (2) relative to the reference TGF-ß inhibition of VEGF stimulated activity. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis.

6. Copies of pages from laboratory notebook showing the positive results for the PRO320 polypeptide (SEQ ID NO:140), identified by Pin number P288-1, in Assay #9 are attached to this declaration (with dates redacted) as Exhibit A. These experiments were performed and the results were obtained prior to February 12, 1999.

7. Exhibit A clearly shows that the polypeptide designated PRO320 was tested, and its ability to inhibit the proliferation of endothelial cells was determined prior to February 12, 1999.

8. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Napoleone Ferrara	Date
Audrey Goddard	Date
Paul J. Godowski	Date
Austin Gurney	Date 7/1/05
William I. Wood	Date

SV 2083152 v1
1/28/05 5:18 PM (39780.2630)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Turner, Sharon L.
Avi J. ASHKENAZI, et al.	)	Art Unit: 1647
Application Serial No. 10/017,191	)	Confirmation No: 6712
Filed: October 24, 2001	)	Attorney's Docket No. 39780-2630 P1C62
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

DECLARATION OF NAPOLEONE FERRARA, Ph.D., AUDREY GODDARD, Ph.D., PAUL J. GODOWSKI, Ph.D., AUSTIN GURNEY, Ph.D., AND WILLIAM I. WOOD, Ph.D. UNDER 37 C.F.R. §1.131

MAIL STOP AMENDMENT
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Napoleone Ferrara, Ph.D., Audrey Goddard, Ph.D., Paul J. Godowski, Ph.D., Austin Gurney, Ph.D., and William I. Wood, Ph.D. declare and say as follows:

1. We are the inventors of the above-identified application.

2. We have read and understood the claims pending in this application, and are aware that the claims have been rejected as anticipated by Ford *et al.*, U.S. Patent No. 6,392,018, filed February 12, 1999 and issued May 21, 2002.

3. We conceived and reduced to practice the invention claimed in the above-identified application in the United States prior to February 12, 1999.

4. At the time the present invention was made, one of the inventors, Napoleone Ferrara, Ph.D., was, as still is, responsible for overseeing the testing of novel polypeptides, including the polypeptide designated PRO320, in endothelial cell proliferation assay (Assay #9, Example 109). This assay is used to find agents that are capable of inhibiting proliferation of endothelial cells.

5. In this assay, bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum 12-14 passages) were plated on 96 well plates at a density of 500 CELLS/WELL per 100 L in low glucose DMEM, 10% calf serum. 2 mM glutamine, lx pen/strept and fungizone, supplemented with 3 ng/mL VEGF. Controls were plated the same way but some did not include VEGF. A test sample of the PRO polypeptide of interest was added in a 100 111 volume for a 200 UL FINAL VOLUME. Cells were incubated for 6-7 days at 37°C. The media was aspirated and the cells washed lx with PBS. An acid phosphatase reaction mixture (100 YL, 0. IM sodium acetate, pH 5.5,0.1 % TRITON-100,10 mM p-nitrophenyl phosphate) was added. After incubation for 2 hours at 37°C, the reaction was stopped by addition of 10 JAL IN NaOH. OD was measured on microtiter plate reader at 405 nm. Controls were no cells, cells alone, cells + FGF (5 NG/ML), cells + VEGF (3 NG/ML), cells + VEGF (3 ng/ml) + TGF-ß (1 ng/ml), and cells + VEGF (3ng/mL) + LIF (5 NG/ML). (TGF-P at a I ng/ml concentration is known to block 70-90% of VEGF stimulated cell proliferation.) The results were assessed by calculating the percentage inhibition of VEGF (3 ng/ml) stimulated cells proliferation, determined by measuring acid phosphatase activity at OD405 NM. (1) relative to cells without stimulation, and (2) relative to the reference TGF-ß inhibition of VEGF stimulated activity. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis.

6. Copies of pages from laboratory notebook showing the positive results for the PRO320 polypeptide (SEQ ID NO:140), identified by Pin number P288-1, in Assay #9 are attached to this declaration (with dates redacted) as Exhibit A. These experiments were performed and the results were obtained prior to February 12, 1999.

7. Exhibit A clearly shows that the polypeptide designated PRO320 was tested, and its ability to inhibit the proliferation of endothelial cells was determined prior to February 12, 1999.

8. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Napoleone Ferrara	Date
Audrey Goddard	Jan. 3/05 Date
Paul J. Godowski	Date
Austin Gurney	Date
William I. Wood	1/28/05 Date

SV 2083152 v1
12/20/04 4:15 PM (39780.2630)